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EXAMINER	
LEAVITT, MARIA GOMEZ	

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1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/578,043	SANDIG ET AL.	
	Examiner	Art Unit	
	MARIA LEAVITT	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09-07-2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1-10,12,14 and 15* is/are pending in the application.

5a) Of the above claim(s) *8-10 and 12* is/are withdrawn from consideration.

6)☒ Claim(s) *7* is/are allowed.

7)☒ Claim(s) *1-6, 14 and 15* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-10, 12, 14 and 15 are pending. Claims1, 3-7 have been amended and claims 14 and 15 have been added by Applicants amendment filed on 09-07-2011. Claims 8-10 and 12 were previously withdrawn from consideration as being drawn to non-elected inventions, there being no allowable generic or linking claim.

Applicants' election with traverse of the following species was previously acknowledged:

1) a viral gene for the combination of cellular genes to immortalize an avian cell line by non-viral transfection as recited in claim 1,

2) a first viral gene that is an adenovirus E1A gene from mastadenoviruses as recited in claim 3 (iv) and the second viral gene encoding for an adenovirus E1B55K protein of all groups as recited in claim 3 (iv) ,

3) a cell line derived from duck as recited in claim 3 (i) ,

4) cells of the retina as the cells subjected to immortalization as recited in claim 3(ii),

5) the E1A gene according to the sequence complementary to bp 4230 to 3113 of SEQ ID NO:9, and the E1B gene according to the sequence complementary to bp 2345 to 550 of SEQ ID NO:9.

A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01. The previous office action was made FINAL by the Examiner. Applicant is reminded of the right to petition under 37 CFR 1.144, if applicant disagrees with the requirements for restriction filed on 07/27/2010.

The examiner acknowledges receiving an executed Declaration under 37 C.F.R. § 1.132 signed by Dr. Jordan on September 05, 2011 ("Jordan Decl."), and filed on 09/07/2011.

Therefore, claims 1-7, 14 and 15 are under current examination to which the following grounds of rejection are applicable.

Withdrawn rejections in response to Applicants' arguments or amendments

Claim Rejections - 35 USC § 112, second paragraph

In view of Applicants' amendment of claim 1 and claims 3 (i) and 4 (i), rejection of claims 3 (i) and 4 (i) under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention has been withdrawn.

In view of Applicants' amendment of claim 3 (i), (ii), (iii) and (iv), claim 4 (i) and (ii), and claim 5 (i), rejection of claim 3 (i), (ii), (iii) and (iv), claim 4 (i) and (ii), and claim 5 (i) under 35 U.S.C. 112, second paragraph, has been withdrawn.

Claim Rejections - 35 USC § 112-Deposit Requirement

In view of the executed declaration by Dr. Sanding with completed statement that the deposit was made under the Budapest Treaty for cell line 12A07-A10 (DSM-ACC2695) along with a statement that "all restrictions on access will be removed on grant of the patent," rejection of claim 7 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement-Deposit Requirement, has been withdrawn.

Remaining objections/rejections in response to Applicants' arguments or amendments

Claim objection

Claim 1 remains objected. Though Applicants have spell out the abbreviations E1A and EIB55K, the term "an adenovirus" should be inserted in front of "early region 1A (E1A) gene" as recited in claim 3(iv) (now subpart iv cancelled) and for specific support in the specification. Appropriate correction is requested.

Claim Rejections - 35 USC § 102

Claim 1 has been amended to recite an immortalized avian cell line comprising a combination of viral genes, at least on first gene affecting the function of the retinoblastoma protein and at least one second viral gene affecting the p53 protein or a family member thereof, wherein the first viral gene is an early region 1A gene from mastadenoviruses and the second viral gene codes for an earlier region 1B55K protein from mastadenoviruses.

Claim 1 is directed to a product by process claim comprising an immortalized avian cell line. The avian immortalized cell line does not require any structure such as expression of the E1A gene or expression of a gene coding for E1B 55K, integration into the cell genome and others. All what is required in the claimed immortalized avian cell line is the structure of being immortalized implied by the means of immortalizing. An immortalized avian cell line may not even require the recited genes. Thus any avian immortalized cell line reads on the claimed invention.

Claims 1 remains rejected under 35 U.S.C. 102(b) as being anticipated by Kim et al. (1995, Oncogene 20: 2671-2682, of record).

Response to Applicants' Arguments as they apply to rejection of claims 1 under 35 USC § 102

At page 10 of the remarks filed on 09-07-2011, Applicants essentially argue that: 1) Kim et al., merely teaches chicken embryo fibroblast (CEF) cells which were non-virally and non-chemically immortalized, 2) thus gene does not teach an immortalized avian cell line which comprises a combination of viral genes, and 3) Kim does not teach the E1A and E1B55K protein from mastadenoviruses. Applicants' arguments have been respectfully considered but have not been found persuasive

Regarding 1), 2) and 3), claim 1 is a product claim. As stated in the paragraph above the only structural limitation required in the claimed invention is the structure implied by the means of immortalizing an immortal avian cell line. Applicants have not provided an example of a structural limitation that was not address, nor any structural limitations added by the recitation of a means of immortalizing comprising a combination of viral genes including the E1A gene a gene coding for E1B 55K. An immortalized avian cell line may not require the recited genes.

Claim Rejections - 35 USC § 103

To the extent that the means of generating an immortalized avian cell line is given patentable weight, the following rejection stands.

Claims 1-6 remain rejected and new claims 14 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bouquet et al., (U.S. Patent 6,255,108, Date of patent July 3, 2001) in view of Kim et al. (1995, Oncogene 20: 2671-2682, of record), and further in view of Pau et al., (U.S. Patent 7,192,759, Date of filing November 26, 1999; see Score search results for

Application 10/578,043) as evidenced by Bagchi et al., (Cell 1991, pp. 1063-1072) and Renee et al., (1992, Nature pp. 82 – 85) .

Bouquet et al., discloses methods and compositions for producing immortalized avian cell lines from primary duck embryo cells such as fibroblasts or epithelial cells for the production of substances of interest (e.g., molecules or viruses for creating diagnostic reagents or vaccines) comprising introducing into host cells a vector which does not exhibit any oncogenic character but which is able to integrate into these cells comprising a gene which is selected for its capacity to induce immortalization. Specifically, fibroblasts derived from duck embryos were transfected with a vector expressing the viral oncoprotein SV40 virus early region (encodes the T and t antigens) which integrated into their nucleus and immortalized fibroblasts to generate immortalized TDF-2A cells (col. 5, lines 23-27; col. 6, lines 1-21) falling within the scope of at least one first viral gene (**claim 1, in part**). Additionally, a vector expressing the bcl-2 gene under the control of the CMV (human cytomegalovirus) promoter was transfected into the immortalized TDF-2A cells to generate the duck fibroblast line TDF-2A bcl-2 in which apoptosis was deferred as related to control cells at confluency (col. 7, lines 14-32), reading on at least a second viral gene affecting the p53 protein or a family member thereof (**Current claim 1, in part**). Additionally, transfection of duck embryos with plasmid vectors and genes, e.g, gene encoding T antigen, integrated within the genomic DNA (col. 2, lines 30-45) (Current **claims 14 and 15**).

Bouquet et al., does not particularly teach an adenoviral E1A and an adenoviral E1B55K protein.

However, at the time the invention was made, Kim et al., suggests a number of non-virally and non-chemically immortalized chicken cell lines generated by simple transfection of a vector. Kim et al., teaches that functional inactivation of the p53 and Rb regulatory pathways are known to be common events for cellular immortalization (abstract). Kim et al., demonstrates diminished steady-state expression of p53 mRNA while dramatically elevated E2F-1 mRNA levels in immortalized chicken embryo fibroblast (CEF) cells and states that dismissed expression of p53 and increased expression of E2F-1 genes seems to be a common event in immortal CEF. Further, the transcriptional activity of E2F-1 can be either stimulated or suppressed depending on its association with Rb (i.e., regulation of E2F-1 activity is Rb dependent). As "The differential expression of both p53 and E2F-1 genes seem to be a common event in immortal CEF cells and could be an early event in the process of cellular immortalization", Kim et al., suggest functional studies involving the downregulation of p53 by expression of antisense p53 mRNA and upregulation of E2F-1 by introduction of exogenous E2F-1 could help determine the direct relationship between genetic alterations of p53 and E2F-1 and cellular immortalization (p. 2677, col. 2) (Current claims 1 and 2, in part).

The combined disclosure of Bouquet et al., and Kim et al., fails to specifically teach an adenovirus E1A gene comprising the sequence complementary to bp 4230 to 3113 of SEQ ID NO:9 which mediates disruption of Rb proteins and E2F transcription factor, and further, an adenovirus gene encoding E1B comprising the sequence complementary to bp 2345 to 550 preventing apoptosis by p53 .

However, at the time the invention was made, immortalization of embryonic retina cells by a gene product of the E1 gene comprising transfection with a plasmid that contained the Ad

serotype 5 (Ad5) E1A- and E1B-coding sequences (i.e. Ad5 nucleotides 459 3510 SEQ ID NO:1) under the control of a promoter was known in the art as evidenced by the teachings of Pau et al., (col. 4, lines 26-34, claim 4: see score search results for SEQ ID NO:9 bp 4230-3113 and bp 2345-550). Furthermore, it was known in the art at the time the invention was made that the adenoviral E1A disrupts RB/E2F complexes (Bagchi et al., 1991, Cell, pp. 1063-1072) and the E1B region of the adenoviral genome encodes a 55-kD protein (E1B 55K) that binds and inactivates p53 contributing to transformation of primary cells (Renee et al., 1992, Nature pp. 82 – 85) (Current claim 4).

Therefore, it would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made in an attempt to establish the interactions between genetic alterations of p53 which expression induces apoptosis with E2F-1 as suggested by Kim, to substitute the vector expressing the viral oncoprotein SV40 virus early region of Bouquet et al., for another first viral oncogene mediating the disruption of complexes of E2F and Rb as taught by Kim, particularly because Kim et al., suggest deregulation of E2F from its association with Rb (thus inactivating the RB product Rb/E2F) to immortalize avian cell lines. Likewise, it would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to substitute the antiapoptotic gene bcl-2 of Bouquet et al., for a second gene affecting the p53 protein or a family member downregulating p53 by expression, particularly because Kim et al., suggest that downregulation of both p53 and E2F/pRB complexes seems to be a common event in immortal CEF cells and could be an early event in the process of cellular immortalization. Furthermore, one of skill in the art would have recognized that the results of the combination of Ad5 oncogenes E1A and E1B encoded by a gene region comprising bp 4230-

3113 and bp 2345-550 of SEQ ID NO:9 would have yielded the predictable results of inducing cell proliferation by disrupting Rb/E2F complexes and inactivating p53, as these interacting pathways where known in the art to be necessary for neoplastic transformation. Moreover, selection of retina cells as primary avian cells for immortalization would be a matter of design of choice. The manipulation of previously identified DNA fragments and cell transformation systems comprising simple transfection of a vector is within the ordinary level of skill in the art of molecular biology. Thus, all of the elements of the claims were known to one of ordinary skill in the art at the time the invention was made and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions and the combination would have yielded nothing more than predictable results to one of ordinary skill in the art at the time of invention.

Thus, in view of the foregoing, the claimed invention, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC §103(a) as obvious over the art.

The cited prior art meets the criteria set forth in both *Graham* and *KSR*, and the teachings of the cited prior art provide the requisite teachings and motivations with a clear, reasonable expectation of success. Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

Response to Applicants' Arguments as they apply to rejection of claims 1-6, 14 and 15 under 35 USC § 103

At pages 11 and 12 of the remarks filed on 09-07-2011, Applicants essentially argue that: 1) none of the references teaches an immortalized avian cell line that comprises viral genes E1A and E1B 55K from mastadenoviruses, 2) while Bouquet discloses immortalization of cells using

viral protein SV40 and non-viral protein (Bcl-2), this disclosure of immortalizing a cell using a single viral protein cannot render obvious use of any viral protein to immortalized any cells, particularly cells of other species, such as avian, 3) Pau et al., merely discloses immortalization using E1A and E1B coding sequences of a human cell line and is silent about effect of E1A and E1B in avian cells, 4) human adenovirus such as mastadenoviruses, exit only in mammals, and have been unable to replicate in avian cells as described in the Jordan Decl., and 5) without some conserved protein sequence, one of skill in the art could not predict the binding activity of E1A and E1B with avian proteins merely from human or mammalian results, particularly in view of the low sequence homology of the mammalian and avian p53 at the N-terminal domain (¶ [7-8] of the Jordan Decl.). Applicants' arguments have been respectfully considered but have not been found persuasive

Regarding 1) ad 2), viral oncoprotein SV40 virus early region encodes the SV40 large T antigen which is capable of transforming mammalian cells. Bouquet et al., discloses that transfection of duck embryos with a vector expressing the viral oncoprotein early region (encodes the T and t antigens) generates immortalized avian cells. So if transformation of avian cells with viral oncoprotein SV40 virus early region generates immortalized cells, transformation of avian cells with a gene encoding any viral protein should be reasonably expected to immortalized avian cells for the same reason a viral oncoprotein early region immortalizes avian cells, both, viral oncoprotein early region and other viral proteins are viral proteins.

Regarding 3), and 4) in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208

USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Moreover, the subject of adenoviral E1A protein and E1B protein immortalizing avian cells is not significantly relevant in view that some of the adenoviral E1A proteins (e.g., 12S) which infect mammalian cells were known to immortalized avian cell as evidenced by the teachings of Guilhot et al., (1993, Oncogene, pp.619-24; Reference A23 in the IDS filed 08/20/2007). Thus the Jordan Decl. provides no reason why either or both adenoviral E1A gene and E1B genes couldn't be expected to immortalize avian cells lines as easily as the 12S adenoviral E1A protein. Further, other human viruses have successfully immortalized avian cells as set forth in the paragraph above. The examiner notes that that there is no evidence of record that replication of adenoviral E1A gene and E1B genes is required for claimed structure of immortalized cells.

Regarding 5) and 6), the fact that the teachings of Kim et al., target the regulation of the retinoblastoma and p53 tumor suppressor proteins which are the same targets of E1A and E1B for immortalization of mammalian cells, provides support for the contention that the process of immortalizing mammalian and avian cells share common pathways regardless of the sequence homology of p53 in chicken and mammalian species. Furthermore, the adenoviral E1A protein (e.g., 12S) was known to immortalize primary avian cells by itself (Guilhot et al., 1993, Oncogene). Moreover, Applicants have not provided convincing evidence of how full or even partial binding of the E1B55K protein to the amino-terminal region of avian p53 contributes to transformation of primary avian cells. Hence, there are not experimental evidences to support the full scope embraced by the claims.

Conclusion

Claim 7 is allowable

Claims 1-6, 14 and 15 are rejected.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

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/Maria Leavitt/

Maria Leavitt
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